§ 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendments

In the Specification:

Please substitute the paragraph beginning on page 21, line 28, with the following paragraph:

C1

FIGURE 1 shows nucleotide (SEQ ID NO:19) (A) and corresponding amino acid (SEQ ID NO:20) (B) sequence of the LAP-mIFNβ construct. The boxed sequence corresponds to the sequence of the MMP cleavage site including linker sequence;

Please substitute the paragraph beginning on page 22, line 1, with the following paragraph:

C2

FIGURE 2 shows nucleotide (SEQ ID NO:21) (A) and corresponding amino acid (SEQ ID NO:22) (B) sequence of the mIFNβ-LAP construct. The boxed sequence corresponds to the sequence of the MMP cleavage site including linker sequence;

Please substitute the paragraph beginning on page 22, line 5, with the following paragraph:

C3

FIGURE 3 shows amino acid sequences of the precursor domain of TGFβ 1 (SEQ ID NO:23), 2 (SEQ ID NO:24) and 3 (SEQ ID NO:25) (human, Hu), TGFβ 4 (SEQ ID NO:26) (chicken, Ck), TGFβ 5 (SEQ ID NO:27) (frog, Fg). Arrows indicate the position of the proteolytic processing resulting in cleavage of the signal peptide of TGFβ 1 and of the mature TGFβs. N-linked glycosylation sites are underlined, as is the integrin cellular recognition sequence (Roberts and Sporn, Peptide Growth Factors and their Receptors: Sporn, MB and Roberts, AB, Springer-Verlag, Chapter 8, 422 (1996));

Please substitute the paragraph beginning on page 22, line 14, with the following paragraph:

C4

FIGURE 4 shows the sequences (SEQ ID NOs:28-100) of protein cleavage sites of matrix metalloproteinases (MMPs) (Nagase and Fields, Biopolymers, 40, 399-416 (1996));

Please substitute the paragraph beginning on page 24, line 17, with the following paragraph:

C5

Double stranded deoxyoligonucleotide coding for the sequence GLY GLY GLY GLY SER PRO LEU GLY LEU TRP ALA GLY GLY GLY SER (SEQ ID NO:1) was designed as follows:

Sense oligo:

5'AATTCGGGGGAGGCGGATCCCCGCTCGGGCTTTGGGCGGGAGGGGGC

TCAGC 3' (SEQ ID NO:2)

C5

Antisense oligo:

5' GGCCGCTGAGCCCCCTCCCGCCCAAAGCCCGAGCGGGGATCCGCCTCC

CCCG 3' (SEQ ID NO:3)

Please substitute the paragraph beginning on page 25, line 11, with the following paragraph:

C6

Sense Primer 5' CCAAGCTTATGCCGCCCTCCGGGCTGCGG 3' (SEQ ID NO:4)

Antisense primer 5' CCGAATTCGCTTTGCAGATGCTGGGCCCT 3' (SEQ ID NO:5)

Please substitute the paragraph beginning on page 25, line 20, with the following paragraph:

C7

Sense primer 5' CGCGGCCGCAATCAACTATAAGCAGCTCCAG 3' (SEQ ID NO:6)

Antisense primer 5' GGTCTAGATCAGTTTTGGAAGTTTCTGGTAAG 3' (SEQ ID NO:7)

Please substitute the paragraph beginning on page 26, line 3, with the following paragraph:

C8

Sense primer 5' CCAAGCTTATGAACAACAGGTGGATCCTC 3' (SEQ ID NO:8)

Antisense primer 5' CCGAATTCGTTTTGGAAGTTTCTGGTAAG 3' (SEQ ID NO:9)

Please substitute the paragraph beginning on page 26, line 11, with the following paragraph:

C9

Sense primer 5' CGCGGCCGCACTATCCACCTGCAAGACTATC 3' (SEQ ID NO:10)

Antisense primer 5' GGTCTAGATCAGCTTTGCAGATGCTGGGCCCT 3' (SEQ ID NO:11)

Please substitute the paragraph beginning on page 26, line 24, with the following paragraph:

C10

Sense primer starting at signal peptide was 5' CGCCCATGGCGCCTTCGGGGCCT 3' (SEQ ID NO:12). This primer has a modified sequence around the initiator ATG to create a Nco1 site.

Antisense primer 5' CCGAATTCGCTGTGCAGGTGCTGGGCCCT 3' (SEQ ID NO:13)

Please substitute the paragraph beginning on page 27, line 7, with the following paragraph:

C11

To avoid processing of the LAP-mIFNβ protein at Arg 278 of LAP, LAP spanning amino acids Met 1-Ser 273 was cloned. This sequence was followed by a flexible linker (GGGGS, SEQ ID NO:14), a putative MMP9 (Peng et al., Human Gene Therapy, 8, 729-738 (1997); Ye et al., Biochemistry, 34, 4702-4708 (1995)) or putative MMP1 (Nagase and Fields, Biopolymers, 40, 399-416 (1996)) cleavage site (PLGLWA, SEQ ID NO:15) and another flexible portion (GGGGSAAA, SEQ ID NO:16) followed by mature mIFNβ (starting at amino acid Ile-22). Embedding the MMP cleavage site in a hydrophilic area should facilitate access to enzymatic attack. The core of the cleavage site (PLGL, SEQ ID NO:17)

has been shown to be cleaved as a peptide by MMP2 and in a different version (PLGI, SEQ ID NO:18) also by MMP3, MMP7 and MMP8 (Nagase and Fields, Biopolymers, 40, 399-416 (1996)) .

C11

Please substitute the paragraph beginning on page 27, line 22, with the following paragraph:

The unprocessed LAP-mIFNβ (SEQ ID NO:20) and mIFNβ-LAP (SEQ ID NO:22) fusion proteins have an expected molecular weight of 52,375 and 51,768 Daltons respectively. The primary sequence of these fusion proteins contains four possible N-glycosylation sites. A schematic representation of the primary structure and putative folding of these proteins and their possible interaction with LTBP is shown in Fig. 5. On the right panel of Figure 5B the folding of LAP-mIFNβ is shown resembling the folding of native TGFβ. Near the amino terminal end (N) of the LAP-mIFNβ, Cys 33 interacts with the third 8-cysteine-rich repeat of LTBP, whilst Cys 224 and 226 are expected to dimerize the protein by intermolecular disulphide bonds (Saharinen et al., Cytokine and Growth Factors, 10, 99-117 (1999)). On the left panel of Figure 5B, the structure of mIFNβ-LAP is shown. Cys 33 is now located behind the MMP cleavage site and Cys 224 and 226 are closer to the carboxy (C) end of the protein.

C12

In the Claims:

Please cancel claims 4 and 18 without prejudice to or disclaimer of the subject matter contained therein.